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REMARKS/ARGUMENTS

Claims 1 to 5, 9 to 29, 62 to 70 and 72 are pending in this application. Claims 6 to 8, 30 to 61, 71 and 73 have been previously canceled. This amendment includes no new matter.

The Examiner rejects claims 1 to 5, 9 to 17, 19 to 29, 62 and 63 under 35 USC 103(a) as being obvious over Dutillio when taken with Sanders and in further view of Mohammed and in further view of Michael. Applicant traverses the rejection.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for a skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination: MPEP §2143.

The Examiner indicates that Ditullio teaches expression of an avian cell *in vitro* with a vector that comprises a nucleotide sequence encoding an immunoglobulin polypeptide since Ditullio teaches that an avian cell can be targeted either *in vitro* or *in vivo*, referencing page 7 to 10 of Ditullio. Applicant disagrees with the Examiner.

It is stated in Ditullio beginning at line 10 of page 7 that: "The cells of the blastoderm are genetically manipulated both *in vitro* and *in vivo* using gene delivery techniques and then used to produce transgenic or chimeric chickens by allowing development in the egg, transferring to a recipient unfertilized egg, or transferring to the testes of a sterile rooster for development into spermatogonia." Contrary to the Examiner's statement, there is no indication in Ditullio that the manipulated blastodermal cells express the introduced transgene. In Ditullio, the blastoderm cells that were supposedly "manipulated" *in vitro* to contain a transgene desired to be incorporated into a transgenic bird were not used, or contemplated for use, to produce an immunoglobulin polypeptide. In particular, there is no indication presented in Ditullio that blastodermal cells which have been manipulated to contain a desired coding sequence could be used to express and secrete a coding sequence product for the purpose of purification. Moreover, blastodermal cells are not oviduct cells.

Furthermore, there is no indication of success demonstrated in Ditullio for the production of a transgenic bird that produces antibodies, or any other protein. Ditullio

has substantial prophetic disclosure, written in the present tense, describing transgenic chicken production and antibody production. However, the only data apparently presented in Ditullio for avian transgenesis shows G0 chicks (i.e., hatched chimeric chicks) which test positive for the transgene DNA in heart, liver and kidney tissue, but no transgene expression of the DNA is shown in bird tissue. Therefore, though Dittulio may disclose various aspects of gene expression such as enhancers, initiation signals, promoters, ect. which can be used for gene expression, there is no evidence presented that heterologous gene expression in any tissue of a transgenic bird including oviduct tissue was enabled by Ditullio. For example, at page 16, lines 8 to 9, of Ditullio, Table 7 is described as representing an "analysis of tissue expression of human insulin transgene in chimeric chickens" but in fact Table 7 only shows results of a PCR analysis of genomic DNA isolated from the chimeric chicks.

In sum, Ditullio is not reasonably applicable to the presently claimed invention from the standpoint of 35 USC 102 or 35 USC 103 since Dituillo does not suggest heterologous gene expression in cultured cells (or teach heterologous gene expression in a transgenic bird).

The Examiner states that prior to the time of the claimed invention Sanders taught utilizing chicken oviduct cell systems *in vitro* to express heterologous genes and that in particular, Sanders taught using tubular gland cells which are primary oviduct cells isolated from chickens which were transfected with various plasmids.

Sanders may demonstrate that the production of a well known reporter protein in an oviduct cell may be possible in order to analyze gene regulatory elements, but this is not indicative that production of useful antibodies is feasible in transfected oviduct cells in culture. Antibodies are different than CAT which is a simple, non-glycosyated, bacterial enzyme that has been shown to be easily produced in functional form in a wide variety of cell types. Sanders does not demonstrate or suggest that a heterologous protein such as a glycosylated immunoglobulin molecule or antibody can be successfully produced in avian oviduct cells in culture. In addition, and importantly, Sanders does not disclose heterologous production of any protein product which is intended to be useful outside of the context of being inside of the oviduct cell where the protein can perform a

specific function and further, of course, Sanders does not disclose or contemplate the purification of such a protein product and as such is not related to the present invention.

The Examiner indicates that prior to the time the claimed invention was made, Mohammed taught expression of recombinant human antibodies in stably transfected DT40 cell lines. In particular, the Examiner indicates that Mohammed teaches that two vectors, one encoding an antibody light chain and the other encoding the heavy chain, were cotransfected into a DT-40 cell line and that the cells were maintained in culture for two days and the surviving colonies were screened by ELISA verifying expression of the antibodies.

It may be true that Mohammad reports DT40 cells that can secrete recombinant immunoglobulin. However, the work of Mohammad does not disclose, teach or even suggest the production of immunoglobulin in avian oviduct cells for the purpose of isolation or purification. Moreover, Mohammad is directed to injecting of recombinant DT 40 cells into chickens for the purpose of producing the antibody in the chicken and is not directed to methods of producing antibodies from the DT 40 cells for isolation or purification and as such is not related to the present invention.

The Examiner states that Michael teaches producing cells that express monoclonal antibodies, wherein the cells are screened for the antibody of interest by, for example, measuring the binding of the antibodies and that Michael specifically teaches *in vitro* transfection of cells, culturing the cells and then isolating the antibody from the cells (the Examiner cites column 3, lines 15 to 27 of Michael). The Examiner also states that Michael teaches methods of producing monoclonal antibodies in an avian system, in particular, chickens. Though the Examiner's characterization of Michael is at least partially correct, Michael is unrelated to the present invention. At column 3, lines 15 to 27, Michael discusses an embodiment of the invention based on well known techniques related to obtaining nucleic acid encoding antibody binding regions from immortalized antibody producing B cells obtained from immunized chickens and reintroducing the nucleic acids into host cells, culturing the cells and isolating the antibody. However, the Michael reference is directed to the production of chicken monoclonal antibodies (not heterologous monoclonal antibodies) and the passage cited by the Examiner does not relate to making a transgenic chicken or to making antibodies in oviduct cells in cultures

but is drawn to chicken antibody production by standard methodologies in host cells and as such is not related to the present invention.

As mentioned by applicant, one of the requirements for a *prima facie* showing of obviousness is that there must be a suggestion or motivation in the art for a skilled artisan to combine the necessary features from the prior art to arrive at the invention. This requirement is not met. What the Examiner does is step through various references citing components of the references that when taken together allegedly constitute all the features of the claims. That is, the Examiner discusses each of the references, cites deficiencies in each reference and moves on to the next reference alleging the deficiencies are cured by the following reference. However, the Examiner points to no motivation for combining the Ditullio, Sanders, Mohammed and/or Michael references to arrive at the claimed invention. For example, the Examiner states that "Dutillio *et al.* differ from the claimed invention in that they do not specifically teach producing the antibody in an avian oviduct cell. However, prior to the time of the claimed invention, Sanders teach utilizing chicken oviduct cell systems *in vitro* to express heterologous genes." In another example, the Examiner states "Although Ditullio teach that the cell can be targeted *in vitro* or *in vivo*, they do not contemplate that the cell can produce an antibody outside of the context of producing a transgenic avian that produces the antibody. However, prior to the time the claimed invention was made, Mohammed teach expression of recombinant human antibodies in stably transfected DT40 cell lines." In still another example, the Examiner states "Ditullio, Sanders and Mohammed differ from the claimed invention in that they do not teach or suggest the expression vector further encodes a second immunoglobulin polypeptide and an IRES (claim 3), that the vector is a viral vector (claims 9-10), and that the promoter is the cytomegaloviral promoter (claim 13), and they do not teach isolation of the immunoglobulin from the cultured cells. However, prior to the claimed invention, Michael teach producing cells that express monoclonal antibodies, wherein the cells are screened for the antibody of interest, by, for example, measuring the binding of the antibodies (co. 2-3, bridging ¶), and specifically teach *in vitro* transfection of cells, culturing of the cells, and then isolating the antibody from the cells (col. 3, lines 15-27)."

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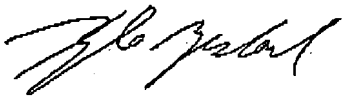
Merely stating that the deficiencies in one reference are found in another is insufficient for a showing of motivation to combine and as such the obviousness rejection is improper and should be withdrawn.

The Examiner also sites Larocca (US Patent No. 6,448,083); Ling (Genomics 60: 341-355, 1999) and Najarfian (Exp. Opin. Invest. Drugs, 9(9): 2147-2167, 2000) under 35 USC 103 rejections of certain dependent claims, when taken in combination with the Ditullio, Sanders, Mohammed and/or Michael references. Applicant traverses these rejections and does not agree with the Examiner's characterizations of these references. In addition, since the independent claims are not made obvious by the Ditullio, Sanders, Mohammed and/or Michael references, as explained by applicant, these later cited references do not make obvious the specified dependent claims.

In conclusion, applicant submits that the claims 1 to 5, 9 to 29, 62 to 70 and 72 are allowable and respectfully requests the Examiner to pass the above-identified application to allowance.

If any issues remain to be addressed in this matter, which might be resolved by discussion, the Examiner is respectfully requested to call applicants' undersigned counsel at the number indicated below.

Respectfully submitted,



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